Proffered Papers

Breast cancer II

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A phase III randomized trial of bendamustinehydrochloride, methotrexate, and 5-FU (BMF) versus CMF as first-line treatment of patients with metastatic breast cancer

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Background: Bendamustine is a bifunctional agent with alkylator and purine-like properties agent that has shown superior antiproliferative *in vitro* effectivity and preliminary improved clinical effect compared to Cyclophosphamide. The replacement of Cyclophosphamide by Bendamustin in the CMF-regimen was prospectively tested in this randomized, phase III pivotal trial.

Patients and Methods: 364 patients with metastatic breast cancer, not previously treated for metastatic disease by chemotherapy have been randomized to either BMF (Bendamustine 120 mg/m*, Methotrexate 40 mg/m*, 5-FU 600 mg/m*) or CMF (Cyclophosphamide 500 mg/m* instead of Bendamustine). The same treatment was given on day 1 and 8, and was repeated on day 29. Primary aim of the study was to improve the time to progression.

Results: A significant difference in median time to progression was observed in favour for the BMF group (8.2 months) compared to CMF group (6.7 months). Moreover, effect of BMF on TTP became highly significant in the stratum "prior adjuvant therapy in patients with non-visceral metastases" (p=0.034). Confirmed clinical responses were observed with equal frequency (19.8% vs 18.0%) in both treatment arms. A non statistically significant difference in t he duration of response of 14.8 (BMF) and 10.3 (CMF) months was recorded (p=0.076). Leucopenia (62.7% vs. 40.0%), thrombopenia (32.0% vs 10.3%) and stomatitis (44.4% vs 24.3%) were more frequent in the BMF arm, whereas alopecia (11.2% vs 17.8), amenorrhea (10.1 vs 17.3%), and constipation (10.7% vs 18.4%), were more frequent in the CMF group. The incidence of CTC grade 4 toxicities was higher in the BMF arm compared to the CMF group, whereas the incidence of grade 3 toxicities was equally distributed (36% vs. 31%). No differences in quality of life between the two treatments was detected.

Conclusions: The substitution of Cyclosphosphamide by Bendamustine in the "CMF" regimen can significantly increase anti-tumor activity in patients with metastatic breast cancer. The modified treatment regimen showed an acceptable toxicity and should be further explored in early stages of this disease.

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Phase III comparison of docetaxel (D)and paclitaxel (P) in patients with metastatic breast cancer (MBC).

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Docetaxel and paclitaxel are among the most active agents for the treatment of patients (pts) with MBC. In randomized studies, the reported response rates for D have ranged from 30-48% and for P (3-hour infusion) from 16-29%. We report the first direct comparison of D to P in pts with MBC after failure of anthracyclines.

Methods: Between 1994 and 2001, 449 women were randomized to either D 100 mg/m2 (1-hour infusion) q 3 wks or P 175 mg/m2 (3-hour infusion) q 3 wks. Eligibility criteria included: bi-dimensionally measurable MBC; and, either 1 prior anthracycline-based regimen as first-line therapy for MBC or disease progression during or within 12 months of completing anthracycline-based adjuvant or neoadjuvant chemotherapy.

Results: The arms were well balanced for (D vs P): median (med) age (56 vs 54); med KPS (90% vs 90%); hormone receptor positivity (56% vs 50%). Intent-to-treat (ITT) analysis was performed for the major efficacy endpoints.

ITT	D (n=225)	P (n=224)	p-value
ORR	32.0%	25.0%	0.10
CR	2.2%	5.4%	
PR	29.8%	19.6%	
SD	38.2%	39.7%	
PD	16.9%	29.0%	
Med TTP	5.7mos	3.6mos	<0.0001
Med OS	15.4mos	12.7mos	0.03

In the analysis of 388 eligible pts evaluable for response, the ORR was D=37.4% vs P=26.4% (p=0.02), and D maintained its statistical superiority in TTP and OS. 444 pts received drug and were evaluable for safety, 222 pts on each arm. Mean and med # of cycles administered was 6.1 and 6 (D) vs 5.8 and 4 (P). Grade 3/4 toxicities for D vs P: neutropenia 93.3% vs 54.5%; asthenia 23.9% vs 6.8%; infection 14.0% vs 5.0%; edema 11.3% vs 4.5%; stomatitis 10.4% vs 0.5%; neuromotor 9.0% vs 4.5%; neurosensory 8.6% vs 4.5%.

Conclusion: The ORR was higher for D than for P, and this difference approached statistical significance in the ITT analysis. TTP and OS were statistically superior for D. Treatment with D was associated with an increased incidence of grade 3/4 toxicities.

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Phase III study comparing AT (Adriamycin, Docetaxel) to FAC (Fluorouracil, Adriamycin, Cyclophosphamide) as first-line chemotherapy (CT) in patients with metastatic breast cancer (MBC)

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Introduction: In a multicenter phase III study we compared the efficacy and safety of six cycles of AT (50/75 mg/m^2) to FAC (500/50/500 mg/m^2) each given on day 1, q3 weeks as first-line chemotherapy in MBC.

Material and methods: The study was performed in 1 academic and 18 community hospitals in the southwest Netherlands. Adjuvant anthracycline treatment up to a cumulative dose equivalent to 240 mg adriamycin/m^2 was allowed. Patients on AT received ciprofloxacin prophylaxis.

Results: Between 03/97 en 04/02, 216 patients were randomized. Patient and tumor characteristics were balanced; median (med) age 53 years, med. performance status WHO 0, adjuvant CT 33%, ≥ 3 tumor sites involved 72%; visceral (lung/liver) disease 67%. Med. follow-up was 22 months.

The only significant difference in severe (III/IV, WHO) toxicity, in the current analysis, is the incidence of febrile neutropenia, AT 34%, FAC 9,7% of the patients (p < 0.001) and 7.5% and 2% of all cycles, respectively (p<

	AT (n=104)		FAC (n=103)
Overall response (OR)	62%	38%	p=0.001
CR	4%	1%	
PR	58%	37%	
CR+PR+SD ≥ 6 months (clinical benefit)	77%	62%	p=0.02
Med. duration of OR (months)	8.3	8.2	
Med. progression-free survival (months)	7.7	7.0	

0.001). There were 2 toxic deaths in the AT arm (1 patient septic). Efficacy results were analysed on intent to treat basis. All responses were subjected to blinded review by the principal investigator.

Conclusion: In this phase III study, AT produced a significantly higher objective response rate than FAC. When clinical benefit was considered the difference remained significant. Median progression-free survival was equal in both arms. Data on overall survival are under analysis and will be presented.

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Randomised phase II trial (M77001) of trastuzumab (Herceptin®) plus docetaxel versus docetaxel alone, as first-line therapy in patients with HER2-positive metastatic breast cancer

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Background: Herceptin administered intravenously (iv) weekly in combination with chemotherapy has been shown to increase survival in women with HER2-positive metastatic breast cancer (MBC). Herceptin is currently licensed for use in combination with paclitaxel and as monotherapy. The taxanes paclitaxel and docetaxel are commonly used in the treatment of patients with MBC. Preclinical data suggest that Herceptin in combination with docetaxel may be as, or even more effective, than Herceptin and paclitaxel. Several small clinical studies have demonstrated good response rates for the combination of Herceptin and docetaxel. Therefore, this promising combination has been investigated in a randomised trial.

Patients and Methods: HER2 testing was performed locally or in a reference laboratory using immunohistochemistry (IHC) or fluorescence *in situ* hybridisation (FISH). Patients (pts) with IHC 3+ or FISH-positive disease (IHC 2+ was allowed at the beginning of the study), and at least one measurable lesion, were eligible. Pts with HER2-positive MBC were randomised to receive Herceptin (4 mg/kg iv loading dose followed by 2 mg/kg weekly until disease progression) in combination with docetaxel (100 mg/m^2 iv every 3 weeks x 6 cycles) or docetaxel alone. Pts on docetaxel monotherapy were allowed to crossover to receive Herceptin on disease progression. Tumour response was assessed according to WHO criteria by the investigator and by an independent radiological review board.

Results: 188 pts were recruited between April 2000 and October 2002; recruitment is complete. 94 pts were randomised to receive Herceptin plus docetaxel, and 94 pts to receive docetaxel alone. Preliminary safety data indicate that Herceptin plus docetaxel was generally well tolerated, with no unexpected toxicities seen to date. The incidence of febrile neutropenia/neutropenic sepsis was 19% (18/94 pts) in the Herceptin plus docetaxel arm versus 16% (15/94 pts) in the docetaxel-alone arm. Two pts died due to septicaemia in the docetaxel-alone arm. Minor asymptomatic falls in left ventricular ejection fraction of uncertain significance were common in this study but only one patient (treated with Herceptin plus docetaxel) developed congestive heart failure (CHF). This patient had received prior adjuvant doxorubicin (cumulative dose 300 mg/m^2) and developed CHF about 5 months after starting Herceptin and docetaxel.

Conclusions: The observed rate of CHF of about 1% to date in M77001 compares favourably with that observed for Herceptin plus paclitaxel. No unexpected toxicities have been seen to date. Results of the primary efficacy analysis will be presented.

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Shorter survival times following adjuvant endocrine therapy in oestrogen (ER) - and progesterone receptor (PgR) positive breast cancer (BC) overexpressing c-erbB-2 or with an increased expression of vascular endothelial growth factor (VEGF)

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Background: Expression of oestrogen- (ER) and progesterone receptors (PgR) is predictive factors for benefit from endocrine therapy. Overexpression of c-erbB-2 and high VEGF have been associated with a worse outcome in retrospective studies, including patients receiving adjuvant endocrine therapy. The worse prognosis seen after endocrine therapy has been claimed to partly be explained by the correlation between high c-erbB-2 and VEGF expression and steroid receptor negativity, and the prognostic value of these factors have in some studies wanished when ER negative patients have been excluded.

Aims: To investigate the possible prognostic value of c-erbB-2 and VEGF in 679 patients with primary breast cancer, including the group of 388 receiving adjuvant endocrine therapy.

Materials and methods: Patients with a diagnosis of breast cancer from 1993 to 1996 at the Karolinska Hospital and St Görans Hospital, Stockholm with cytosols after determination of steroid receptors were included (n=679). Of these, 423 had a node-negative BC, 200 a node-positive BC, in 56 patients was axillary disection not performed. The median age was 64 years (range 33 to 89), and the median follow-up time was 94 months. Adjuvant therapy was given to 573 patients; endocrine mostly tamoxifen +/- radiotherapy (RT) (n=388), only RT (n=98), or chemotherapy +/- RT +/- endocrine therapy (n=87). VEGF and c-erbB-2 status were determined by enzyme immuno-sorbent assays (ELISA). In 200 patients, c-erbB-2 status was also determined by immunohistochemistry (IHC) with the monoclonal antibody CB11.

Results: Overexpression (+3) of c-erbB-2 by IHC was found in 12% of the tumours. Correspondingly the 12% with the highest c-erbB-2 values by the ELISA were classified as overexpressers. Overexpression of c-erbB-2 was associated to higher VEGF content (p=0.004). Both c-erbB-2 (RFS p=0.03344, OS p=0.02176) and VEGF (RFS p=0.00779, OS p=0.00187) were significantly related with shorter survival in the total population. Other factors correlated with survival were tumour size (RFS p<0.0001, OS p<0.0001), nodal status (RFS p<0.0001, OS p<0.0001), ER- (RFS, p=0.00150, OS p=0.02792), PgR (RFS p=0.00779, OS p=0.00875), and menopausal status for OS (p=0.00050), but not for (RFS p=0.99119). Patients with high VEGF or c-erbB-2 positive BC receiving adjuvant endocrine therapy (n=388) had significantly shorter survival; c-erbB-2 (RFS p=0.01259, OS p=0.02162), VEGF (RFS p=0.01545, OS p=0.00482). The results remained when only ER and PgR positive patients were included in survival analyses (n=317); c-erbB-2 (RFS p=0.00713, OS p=0.00268), VEGF (RFS p=0.01363 OS p=0.00570) respectively.

Conclusion: Overexpression of c-erbB-2 or higher VEGF expression adds in this retrospective analysis information concerning patients outcome after adjuvant endocrine therapy in ER and PgR positive BC. Results from multivariate analysis will be presented.

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Topoisomerase II alpha (TOP2A) alterations as a predictive marker for epirubicin sensitivity in 805 high-risk breast cancer patients. A randomised DBCG Trial (DBCG89D).

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Background: The purpose of this study was to evaluate *TOP2A* as predictive marker for the efficacy of epirubicin in the adjuvant setting of breast cancer patients. Inhibition of topoisomerase IIα is the primary cytotoxic action of the anthracyclines and it is hypothesised, that copy number changes of the *TOP2A* gene would lead to an altered sensitivity to treatment with epirubicin.

Material and methods: Nine-hundred-and-sixty-two pre- and postmenopausal high-risk patients were enrolled in the protocol DBCG 89D between January 1990 and November 1999. The patients were randomly allocated to either 9 x CMF (cyclophosphamide 600 mg/m^2, metrotrexate 40 mg/m^2 and 5-flurouracil 600 mg/m^2) every 3 weeks (n=495) or 9 x CEF (cyclophosphamide 600 mg/m^2, 5-flurouracil 600 mg/m^2 and 60 mg/m^2 epirubicin) (n=467). Paraffin-embedded tumour-tissue was available from